EVREN TECHNOLOGIES

POST-TRAUMATIC STRESS & TRANSCUTANEOUS VAGAL NERVE STIMULATION

Summary

This white paper presents the burden and neurobiology of Post-Traumatic Stress Disorder (PTSD) and the rationale for treating PTSD using vagal nerve stimulation (VNS). It will review the science and literature on VNS use in treating PTSD and the positive clinical study data using Evren's Phoenix® stimulation device. The Appendix summarizes additional literature on the effects of VNS on a wide range of PTSD symptoms, such as hyperarousal, fear extinction, anxiety, depression, and sleep disturbances.

Post-Traumatic Stress

Cause and Consequences: Post-Traumatic Stress Disorder (PTSD) is a devastating psychiatric condition. It is a complex mental disorder caused by exposure to one or more traumatic events, leading to dysfunctional memory processes that trigger fear responses when there is nothing to fear. People with PTSD often have nightmares, difficulty sleeping, persistent frightening flashbacks, pathologically intense outbursts of anger and anxiety, dissociation, and social avoidance. In short, it leads to a severe reduction in quality of life. The symptoms of PTSD are clustered into four categories: (1) intrusion symptoms (2) avoidance symptoms (3) negative alterations in cognition and mood and (4) alterations in arousal and reactivity.

Co-morbidities and Cost: Individuals with PTSD are at increased risk of depression, anxiety, addiction, early cognitive decline, cardiovascular disease, alcoholism, eating disorders, and homelessness. In one study, 60% of men and 44% of women with diagnosed PTSD were found to meet the diagnostic criteria for three or more other psychological disorders.[1] The risk of suicide can be up to 13 times higher than those without PTSD,[2] and studies have shown rates of PTSD and substance abuse disorders as high as 25-59%.[3] Overall, PTSD has been associated with a 3.8-fold increased risk of death.[4]

PTSD results in higher healthcare costs, and a significant increase in healthcare utilization across all medical services, including primary care, inpatient services, ancillary services, and emergency services.[5] In one study, overall costs of PTSD were found to be three times higher than costs for controls.[6] Given that the risk of suicide for PTSD patients is up to 13 times that of non-PTSD patients, and that the direct medical costs of suicide and suicide attempts was $1.6 billion in 2013 alone, the savings to payers in averted suicide attempts alone would be significant.[7]

***Need*:** Unfortunately, treatments for PTSD are often ineffective, have significant side effects, and high dropout rates.[4] Pharmacotherapies, primarily SSRIs, generally result in a reduction of symptom severity rather than achieving remission.[6,8,9] Exposure Therapies for PTSD are "strongly recommended" by the American Psychological Association,[6] but not all patients respond well to Exposure Therapies. Many will continue to experience symptoms even after therapy,[7] and a majority will experience symptomatic relapse months or years after therapy.[8] The average dropout rate is 36% (ranging from 28% to 68%)[9], which is not surprising since avoidance is a common symptom of PTSD. Behavioral health clinicians and their patients have a grave need for a new solution, especially one that does not include the side effects associated with current pharmacological or cognitive therapeutic solutions.

Vagus Nerve and Vagal Nerve Stimulation (VNS)

PTSD is recognized as dysfunction in the human nervous system, and more specifically, the autonomic nervous system (ANS), which regulates body functions on a largely subconscious level like. breathing, digestion, blood pressure, heartbeat, hormonal regulation, and the dilation or constriction of blood vessels. The ANS consists of three nervous branches: the sympathetic, parasympathetic, and enteric. The enteric nervous system governs the functions of the gastro-intestinal tract and is not our

focus. However, the sympathetic and parasympathetic nervous systems are central to how the body deals with stress/fear response and, therefore, how PTSD manifests and can be treated.

The sympathetic nervous system acts like a car's gas pedal. It triggers the "fight or flight or freeze" response so that the body can respond to danger. The parasympathetic nervous system serves as the body's "stop and restore" mechanism, hence, it is sometimes referred to as the "vagal brake." It promotes the "rest and digest" response that calms the body after a triggered sympathetic response.

The vagus is the largest nerve in the ANS, and its primary function is to regulate the parasympathetic nervous system. The vagus reaches important components of the brain, stimulating synaptic activity while dampening the sympathetic stress response. Vagal tone is an internal biological process that represents the activity of the vagus. Increasing vagal tone activates the parasympathetic nervous system, and having a higher vagal tone means the body can relax faster after stress. Stimulating the vagus increases vagal tone, so VNS can invoke parasympathetic response for someone who, because of trauma, has a diminished ability to do so. Thus, the vagus directly affects how the parasympathetic nervous system operates in the body. This effect is critical to our therapy due to its ability to balance sympathetic and parasympathetic activity.

Two branches of the vagus have been targeted for stimulation. VNS has been performed at the left cervical branch, as seen with implanted technology (iVNS), and at the auricular branch, as seen with transcutaneous auricular vagal nerve stimulation (taVNS) which stimulates the vagus through contact points in the pinna of the ear. The auricular branch of the vagus is composed entirely of afferent vagal nerve fibers, sending signals directly to the brain and permitting a non-invasive treatment with no known serious adverse or off-target side effects.[10]

iVNS and taVNS are distinctly different methods of targeting the vagus, and both have been extensively studied for their effects on the nervous system and the brain. Despite these differences, both exhibit similar activation patterns in the brain[11–14] and have been used to treat the same conditions (such as epilepsy) with similar effect sizes.[15] Thus, clinical evidence of improvement in PTSD-type symptoms in trials using iVNS support the use of taVNS for improvement of such symptoms. Both iVNS and taVNS stimulations are transported by the vagus into the medulla oblongata and to the nuclei tractus solitarii. This nuclear region has multiple projections to many subcortical brain regions implicated in neuropsychiatric disorders,[16–18] providing the physiological basis for a clinically effective device.

The main difference between transcutaneous VNS and iVNS is the safety profile. Because iVNS requires a surgical implant, there are surgically-related serious adverse events and off-target effects from the neck placement, such as coughing during stimulation, croakiness, and general operational and anesthesiologic risks,[19] including infection, vocal cord paresis, and lower facial weakness. On the other hand, a systematic review of safety and tolerability of transcutaneous VNS showed that the technology was both safe and well-tolerated.[10]

Regarding dose, iVNS patients typically receive stimulation all day long in an on/off cycling pattern (e.g., one minute on, five minutes off). This has the benefit of being active during decreased parasympathetic activity, but it only stimulates a fraction of the time when it might be needed most. This method of administration was selected to alleviate some of the unique side effects of iVNS due to off target activation of muscles and nerves in the throat and neck. taVNS has typically been trialed in longer, constant stimulation doses (e.g., one hour on, twice per day) but the doses are not likely to be administered when parasympathetic activity is depressed, thus lowering the potential effect size. Both taVNS and iVNS administration methods appear to have clinically significant effects despite the weaknesses in dosing.

Neurobiology of PTSD

It is common for individuals to experience a heightened or prolonged sympathetic state after a significant trauma. This is associated with increased emotional reactivity, anxiety, and a heightened sensitivity to perceived threats. For many, this is a temporary state lasting days or weeks and is diagnosed as Acute Stress Disorder. For those who go on to develop PTSD, this increased sympathetic

arousal and chronic stress state induces significant changes in physiology that can perpetuate the condition for years.

As Dr. John Williamson, one of Evren's scientific co-founders has said, "PTSD is a reaction to trauma that results in a chronic perception of threat in the environment, eliciting a sustained pathologically aroused state." The nervous system continuously monitors and evaluates risk in the environment, but patients with PTSD have a greater propensity to move from a neutral state to a hyper aroused state, and to stay in that state longer than healthy controls. A person with PTSD may consciously understand that a situation is safe but may be unable to shift to the appropriate physiological state because there is a disconnect between their conscious appraisal and their neurophysiological reaction.[20]

Stress results in acute and chronic changes in specific brain regions and neurochemical systems within the body. Moments of stress or danger cause the amygdala to send a signal to the hypothalamus. This signal activates the hypothalamic-pituitary-adrenal (HPA) axis which regulates immune function and results in higher levels of cortisol, and norepinephrine.[21] Cortisol results in the activation of the sympathetic nervous system, leading to the fight or flight response. Norepinephrine neurotransmitter cells begin in the brain stem, specifically the locus coeruleus, and project into other brain regions such as the amygdala, prefrontal cortex, and hippocampus. These brain regions are involved in the regulation of emotion, motivation, thoughts, learning, and memory. (An increase in norepinephrine in these brain regions incites fear and anxiety behaviors.[22] These behaviors are the natural response to sympathetic arousal and the fight or flight response.

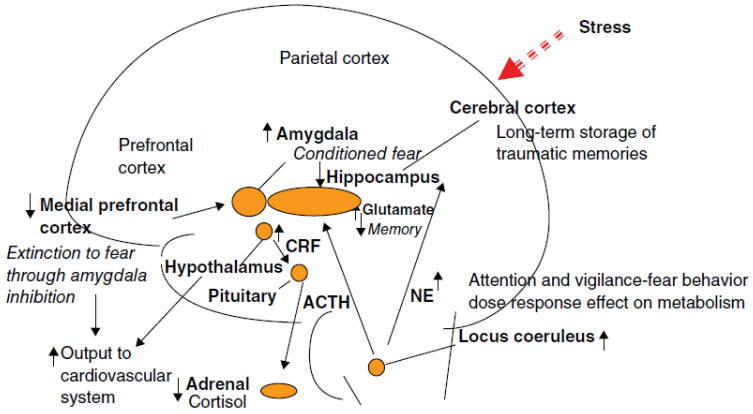

Figure 9.1 Neurotransmitters in posttraumatic stress disorder (PTSD). Neurotransmitters involved in the stress response and PTSD symptoms include norepinephrine (NE), with cell bodies in the locus coeruleus and projections to the amygdala, hippocampus, prefrontal cortex, and hypothalamus, and the hypothalamic–pituitary–adrenal (HPA) axis, with corticotropin-releasing factor (CRF) release from the hypothalamus, which stimulates adrenocorticotropic hormone (ACTH) release from the pituitary, and cortisol from the adrenal. (*See color plate section for the color representation of this figure.*)

Credit: Bremner JD, ed. *Posttraumatic Stress Disorder: From Neurobiology to Treatment*. Ref. #22

The constant state of sympathetic arousal in PTSD patients results in physiological changes to the brain. Changes in brain structures such as the amygdala, prefrontal cortex, and hippocampus have been recorded in people with PTSD.[22] Specifically, PTSD is demonstrated with an increase in amygdala activity resulting in an overactive HPA axis and fear response.[23,24] The prefrontal cortex works alongside the amygdala in helping to regulate emotion. The prefrontal cortex is also involved with decision making and thinking. In a health brain the prefrontal cortex responds to the amygdala's trigger of emotion with rational thinking and decision making. However, PTSD is associated with lower prefrontal cortex volume and activity.[23] This lower volume contributes to the inability to regulate emotions effectively. The hippocampus plays a role in memory encoding, stress response, and fear conditioning. On average, people with PTSD have smaller hippocampi than people without PTSD.[23] This smaller volume leads to dysfunctional memory processing and encoding. This overactivity of the amygdala paired with decrease hippocampus volume leads to the maladaptive and persistent threat detection characteristic of PTSD

These brain changes are also reflected in neurochemical systems throughout the body. Our immune system regulates inflammation within the body and is controlled by the brain structures altered in PTSD. An increase in amygdala activity results in altered signals being communicated with the hypothalamus and thus the HPA axis. Excessive inflammation results from insufficient regulation of immune function. People diagnosed with PTSD have been found to have an increase in inflammatory

markers such as interleukin-6 (IL-6), interferon (IFN), and Tumor Necrosis Factor alpha (TNF alpha) in the blood.[21,25]

The symptoms of PTSD are the psychological and physical representation of the stress-induced changes in these brain areas and the neurochemical systems. Changes in the amygdala and hippocampus help to explain symptoms like intrusive memories of the traumatic event, and distressing memories or thoughts. Decreased prefrontal cortex volumes can result in difficulty regulating emotions, and are associated with comorbidities like anxiety and depression. Chronically increased norepinephrine levels are associated with hyperarousal. Increased inflammation has been linked to depression, cardiovascular disease, and other common comorbid health conditions. These changes also help to explain the inability of SSTR's or exposure therapy to alleviate PTSD symptoms more widely in those suffering from PTSD. The neurological and physiological changes are not addressed by simply increasing serotonin levels, and it is unsurprising that those with PTSD struggle to change the fear- and trauma-based behaviors in therapy without first addressing the underlying physiology.

VNS in PTSD

Vagal Nerve Stimulation addresses the underlying physiological changes involved with PTSD. Since the vagus projects through the nucleus tractus solitarius and the locus coeruleus (LC) extending to the hypothalamus, amygdala, hippocampus, and prefrontal cortex, it is directly involved in the sympathetic hyperarousal in PTSD.[22] Through stimulation of the vagus, these brain areas and subsequent neurochemical systems are activated and reregulated. The vagus works to decrease the sympathetic response and boost the parasympathetic response to restore the balance of the autonomic nervous system.

Fear Extinction

Pathologically intense intrusive and spontaneous memories of traumatic events and the avoidance of these memories are common symptoms of PTSD. The emotional state behind these memories makes them deeply connected in the brain. Extinction of the fear and emotional ties to these memories requires the creation of new memories that override the traumatic ones within the brain. VNS has been found to accelerate the fear extinction process through increased release of norepinephrine in the amygdala and prefrontal cortex.[26] Due to the boost in parasympathetic response caused by VNS and the functionality of the amygdala and the prefrontal cortex, new memories are created.

Amygdala/Hippocampus

Due to the overall general decrease in activity in the amygdala and hippocampus, declarative memory dysfunction is a common problem in PTSD patients.[27] The mediation of neurohormones like cortisol and epinephrine by the vagus in the hippocampus and amygdala, allows for increased memory formation and retention.[27,28] This increase in memory function aids in the creation of new memories and fear extinction learning.

Serotonin (5HT)

As VNS increases norepinephrine in the amygdala and the prefrontal cortex, serotonin (5HT) cell bodies in the dorsal raphe are also activated.[29] This results in secondary effects on the same brain regions as norepinephrine. Therefore, the increase in serotonin due to VNS has a similar effect to SSRIs without the negative effects of desensitization to serotonin receptors.[30]

Hypothalamus/HPA Axis

Vagal afferents project to the hypothalamus and activate the HPA axis.[22] VNS treatment increases HPA axis activation helping to rebalance the sympathetic/parasympathetic tone after a stress response. Therefore VNS in PTSD patients restores homeostasis to the dysregulated HPA axis.[31]

Prefrontal Cortex

The prefrontal cortex is known to be involved in social and cognitive functions. Brain pathways for executive functions such as decision making, planning, thinking, and emotional control are located within the prefrontal cortex. The regulation of negative emotion relies on the interaction of the prefrontal cortex with the amygdala and hippocampus. The communication between these brain areas is stunted in PTSD patients. VNS treatment is known to increases norepinephrine in neurons projecting

from the LC to the amygdala and into the prefrontal cortex. This increase repairs the stunted connection and revives the regulation of negative emotion through the prefrontal cortex.

Inflammation

The vagus also plays a key role in the regulation of cytokines response to stress. Cytokines such as, IL-6, IFN, and TNF alpha, help signal the immune system to increase or decrease inflammation. An influx of cytokines leads to excessive inflammation which is often found in PTSD patients. Stimulation of the vagus regulates these cytokines to a more normal level. Inflammation markers previously demonstrated to increase in patients diagnosed with PTSD are found to have decreased with after VNS treatment.[25] Depression and anxiety have been associated with increased inflammation and it has been hypothesized that this effect may be bidirectional.[32–34]

VNS shows promise in other psychiatric disorders such as depression, anxiety, insomnia, epilepsy, and more. See the appendix to read more about these disorders and how VNS can help improvement.

The Phoenix Technology

Evren's innovative technology utilizes taVNS and is administered using a closed loop algorithm that monitors physiologic parameters and adjusts stimulation based on this input. The Phoenix will apply stimulation when it is needed, at the full potential dose, providing full therapeutic effect while avoiding potential habituation.

We conducted a single arm unblinded, longitudinal, 2-month pilot trial to evaluate comfort level, study compliance, and effect on symptom severity scores in a PTSD population using the Evren Echo Prototype take-home vagal nerve stimulator. The pilot trial included 12 participants with a confirmed PTSD diagnosis by the PTSD Checklist for the DSM-5 and a clinical interview with a neuropsychologist, Dr. Richard Marshall. While PTSD is not confined to the military many veterans struggle with PTSD. Our study reflects this large population with eight of our participants being US military veterans with all eight attributing their PTSD to events occurring during active duty, and four were combat related. In addition, four of the participants had a Traumatic Brain Injury (TBI) during or before their traumatic event.

Participants were directed to use the device twice daily morning and evening for 30 minutes each session. Within the taVNS literature, investigations have been performed on multiple ear locations and stimulation parameters. Two things should be noted about this: reasonable effect sizes have been demonstrated over a wide range of parameters and locations, and over time the literature has moved toward a consensus on the most effective parameters. We believe that our closed-loop taVNS device implementing stimulation based on the direct physiologic metric of parasympathetic activity (respiratory sinus arrhythmia or RSA), using the most recent literature results, will at least match, if not outperform, the results seen with parameters used in the current taVNS literature.

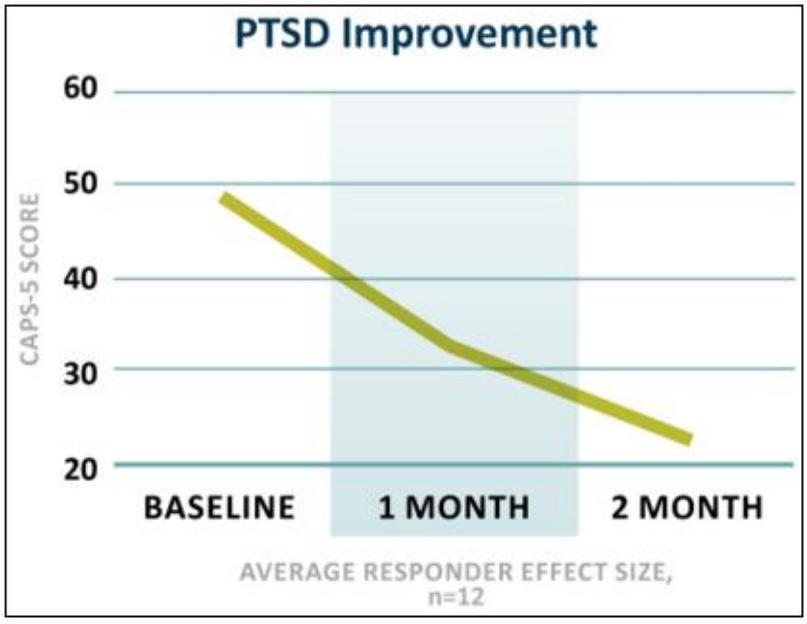

Figure 1 - Responder effect size when averaged among all trial participants.

The CAPS-5 assessment and PROMIS-29 were used to measure improvement in PTSD

symptoms. The CAPS-5 is a widely considered the gold standard scale for symptom severity measurement. This 30 question assessment measures symptoms over one month and is scored between 0 and 80 points. The PROMIS-29 is a self-report questionnaire that assesses Quality of Life (QOL) over seven domains. The CAPS-5 assessment and PROMIS-29 were conducted before the study began and at the end of the first and second month of device use.

The results of this pilot trial were compelling. Participants demonstrated an average 10.9-point reduction in CAPS-5 scores at month 1 (paired t-test P=0.0206 95%CI 2.0 – 19.8) and an 18.8-point reduction at month 2 (paired t-test P=0.0013 95% CI 9.2 – 28.5) (Figure 1, *see above)*. Three study participants achieved full remission levels (CAPS-5 Score <12) and seven no longer met the full CAPS-5 diagnostic criteria for PTSD at two months. Only one participant was considered a non-responder with a CAPS-5 reduction of <6 points (Figure 2).

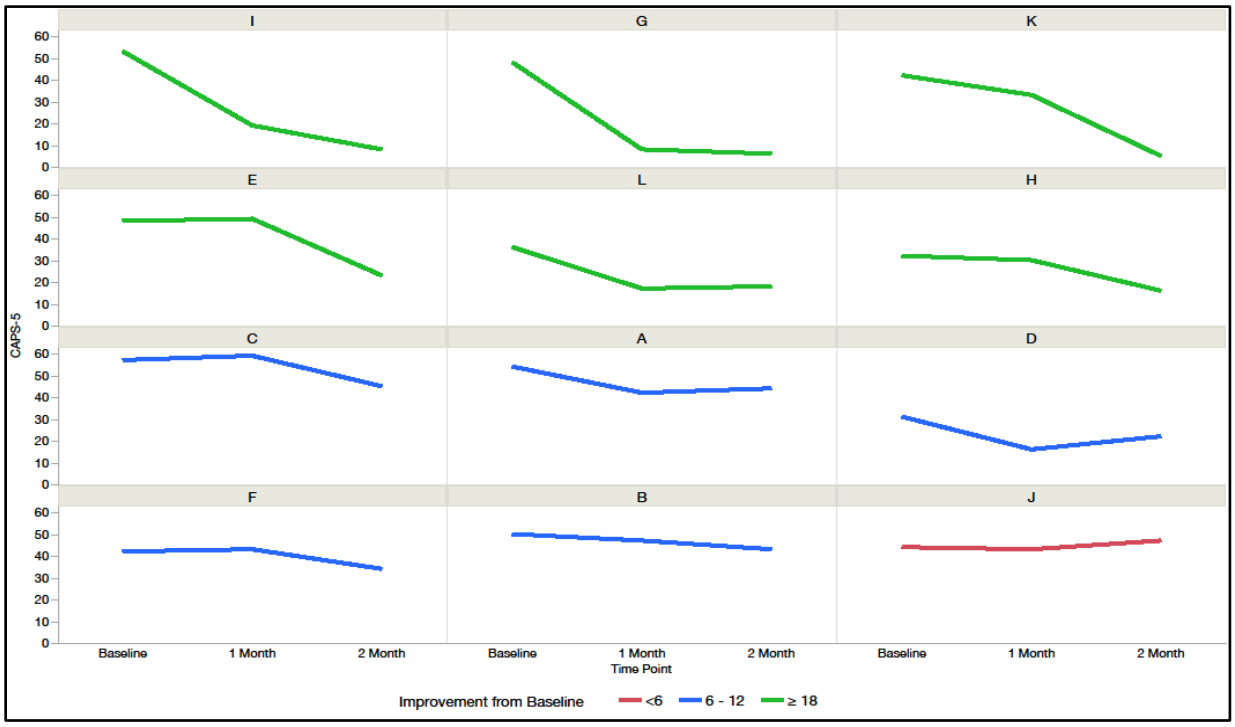

Figure 2 – The average CAPS-5 scores at baseline, 1 month, and 2 months for the 12 study participants charted individually and sorted from largest response (top left) to lowest response (bottom right). Red indicates a treatment non-responder, blue represents a clinically meaningful response, and green is a large response to treatment.

In our study population, the change in quality of life (measured by the PROMIS-29 questionnaire) from baseline to two months showed statistically significant improvement in five of the seven domains using a paired t test (Anxiety/Fear -9.1, 0.0021; Depression/Sadness -5.9, 0.0294; Fatigue -7.6, 0.0036 Sleep Disturbance -9.23, 0.0038; Ability to Participate in Social Roles/Activities +5.6, 0.0257). Small improvements were seen in both pain interference and physical function but they did not reach statistical significance. Many PTSD treatments only address symptoms and fail to improve overall quality-of-life.[35,36] Our results may indicate broader functional improvements due to this treatment method over simply addressing symptoms.

Our study compliance was good, with 11 out of 12 participants compliant with the study procedures (<50% device use). In a questionnaire after the completion of the study, all participants enjoyed using the device, felt that it positively impacted their symptoms, and would continue using the device if able after the end of the study including the one non-responder. No adverse side effects were reported during use of the device.

Although our study was neither powered nor designed to look at comorbid TBI, we did see a drastic change in this population. The study group contained four participants with a TBI, and three of

them achieved improved CAPS-5 scores consistent with full PTSD remission. Even with these small numbers, the CAPS-5 score improvement compared to the non TBI subjects was marginally significant at month 1 (t-test p=0.06) and month 2 (p=0.07). The increased inflammation, decreased neuroplasticity, and profound autonomic dysregulation associated with a moderate TBI could help to explain the treatment effect seen in this small subgroup. These results are worth further investigation, especially given that PTSD risk is elevated in people with history of TBI and they often have reduced treatment efficacy with current therapies.

Overall, in our pilot trial we had a 92% response rate and a significant improvement in quality-of-life measure, especially those with comorbid TBI. Most importantly, every single patient wanted to keep the device, including the patients that achieve complete remission. Based in part on these results, Evren received a Breakthrough Device Designation from the FDA in 2021 for the Phoenix technology. Breakthrough Device Designation indicates that the device may demonstrate substantial improvement on a clinically significant endpoint over the current standard of care in a life threating condition. The PTSD population has historically proven to be a difficult population to work with and often has low compliance rates. The protocol adherence and satisfaction with the device demonstrated in this pilot study indicate that taVNS is feasible and well accepted for extended home use and could be widely adopted by a wider PTSD population.

Conclusion

PTSD is a complex disorder that stems from a significant trauma and results in profound changes in physiology including several brain regions and hormonal systems. This perpetuates dysfunctional memory processes that trigger a sympathetic fear response when there is nothing to fear. This sympathetic response reflects an imbalance in the autonomic nervous system, with a hyperaroused sympathetic system and a diminished parasympathetic response.

The vagus directly regulates how the parasympathetic nervous system operates. Specifically, it addresses the problems created by physiological changes in the specific brain areas and neurochemical systems affected by PTSD. Through stimulation of the vagus, we can rebalance the autonomic nervous systems by increasing the parasympathetic response.

Evren has developed a technology that delivers electrical stimulation through the skin of the ear targeting the vagus. The pilot trial that demonstrated the safety and usability of Evren's technology, resulted in a 92% response rate, and significantly improved quality of life measures. Most importantly, all participants wanted to keep the device upon completion of the study.

Appendix A

Proven Results: VNS Effect on PTSD Symptoms

Multiple pre-clinical and clinical studies have shown VNS and taVNS to significantly improve the symptom clusters of PTSD. One symptom cluster, arousal (resulting from an imbalance in the sympathetic/parasympathetic elements of the autonomic nervous system), responded well to both implanted VNS and taVNS. A second symptom cluster, negative cognition and mood, typically experienced as anxiety (resulting from maladaptive fear extinction) or depression, also has sound clinical results from both implanted VNS and taVNS. Additionally, implanted VNS has been approved as a therapy for treatment resistant depression for years.

Other studies on the treatment of PTSD with VNS (both implanted and transcutaneous) in both human and murine models, all show significant positive results. Researchers at The University of Texas at Dallas, for example, are exploring how implanted stimulation of the vagus helps alleviate symptoms of PTSD when paired with exposure therapy.[37] Other Dallas studies have shown on average a 2.5x improvement, although they have not progressed beyond animal testing in a severe PTSD rat model.[38]

Quality of Life (QOL)

Patients with PTSD are likely to experience poorer functioning and lower objective living conditions and satisfaction.[39] The impact of PTSD on patients' subjective satisfaction and functioning in both the long term and short term is profound.[40] The strongest predictors of lower quality-of-life scores in PTSD patients are arousal symptoms and anxiety or depressive symptoms.[36] In another study, hyperarousal was the only symptom cluster that showed an association with subjective quality of life.[35] There is evidence that iVNS improves quality of life scores in medically intractable epilepsy, without regard to a reduction in seizure frequency, decreased severity of seizures, or increased level of energy alertness.[41] iVNS also improves quality of life in patients with treatment resistant depression,[42] and, when used as an adjunct to treatment as usual in treatment resistant depression, led to significant improvements in quality of life that was sustained through the five years of observation.[43] The results are not just limited to iVNS, a two-week study of taVNS on 29 individuals over the age of 55 demonstrated an increase in quality of life, mood, and sleep.[44]

Given that VNS has been shown to improve quality of life in three distinct patient groups and that taVNS has been shown to have positive effect on hyperarousal,[45] the main component of poor quality of life in PTSD, we believe that taVNS will improve quality of life in PTSD patients.

Depression

Clinical improvement of depression (negative cognitions and mood symptom cluster) was shown in humans when treated with taVNS.[46–48] iVNS has been FDA approved since 2005 for Treatment Resistant Major Depressive Disorder that has not responded to at least four antidepressants. The iVNS literature not only shows significant recovery rates but also indicates that the percentage of responders increases steadily over time.[49–53]

Anxiety

PTSD patients are deeply affected by anxiety symptoms and often manifest anxiety symptoms in very disruptive and problematic avoidance behaviors. iVNS has been successfully tested on severe anxiety disorders including two severe PTSD patients.[17] taVNS has also shown positive results on anxiety disorders although no PTSD patients were tested.[46] taVNS and iVNS have also been shown to reduce the anxiety subscale symptom measures.[42,47,54,55] A study on 97 high-worrying subjects demonstrated that the taVNS group had significantly fewer negative thought intrusions in a pre-worry period than a sham control. This decreased intrusive worrying effect, although not tested in the PTSD population, is

especially promising as intrusive negative thoughts are one of the four primary symptom clusters listed in the DSM-5 and a hallmark of anxiety symptoms.

Social Function

A major symptom of PTSD is poor social functioning and social engagement. This phenomenon is partially explained by the polyvagal theory.[56] In this widely accepted theory, social functioning is directly related to the functioning of limbic brain structures and is heavily influenced by parasympathetic activity. The ability of VNS to improve social function in PTSD patients has not been directly studied but ancillary evidence exists. iVNS has been shown to increase the subscale measure of social function in major depressive disorder patients. This effect was seen even in the non-responder portion of the patient population.[43,52,53,57] iVNS has also been shown to improve the social functioning in patients with autism spectrum disorders.[58,59] One study on healthy controls demonstrated that taVNS can enhance the recognition of emotions in faces.[60] This evidence supports both the Polyvagal Theory and the concept that vagal nerve stimulation can improve social function.

A recent study has demonstrated that both abnormally low and abnormally high parasympathetic activity as measured by RSA negatively impacts prosocial behavior.[61] Our closed loop technology is directly based on the concept of stimulating to increase instances of low RSA and turning off stimulation at normal physiologic levels.

Sleep

One of the more pervasive and problematic issues that plague PTSD sufferers is centered on sleep difficulty. People with PTSD tend to have disrupted sleep patterns and commonly experience recurrent, deeply disturbing, nightmares. It has been well established in the iVNS field that stimulation improves sleep, but there are some downsides when stimulation runs throughout the night, which confounds the data. Previous studies have confirmed that hyperarousal is the key mechanism for insomnia,[62] and a recent study has provided strong indications that taVNS would have beneficial effects on insomnia. Two taVNS studies have measured improvements in sleep as a secondary outcome, one in patients over the age of 55 and the other in patients with depression.[44,46] Finally, results from our pilot trial of the Phoenix prototype in PTSD patients showed significant improvements in sleep for the participants.

Fear Extinction

Prolonged Exposure therapy (including Cognitive Behavioral Therapy, Cognitive Processing Therapy, and other forms of exposure therapy) is the major non-pharmacological practice aimed at treating PTSD. Once a fear has been "learned" or imprinted on the brain the neural circuits have been largely considered permanent. In the case of PTSD this can often happen because of a single deeply emotionally-charged event. The process of Exposure Therapy is to imprint or learn a new neural pattern that establishes the fear as non-threatening. This process is typically very difficult for PTSD patients and can take a very long time. taVNS has three distinct advantages for improving this process. Firstly, taVNS reduces stress response[63,64] and could help the patient more easily endure difficult therapy sessions. Secondly, we believe that our closed loop system will naturally generate an Exposure Therapy situation whereby stressful events will be paired with increased parasympathetic activity via stimulation. This will automatically give the body and mind safety cues during stressful events helping to reinforce the fear extinction learning process. Lastly, taVNS enhances neuroplasticity and therefore increases the fear extinction learning process. This last mechanism has been repeatedly tested in rat models of severe PTSD,[38] and taVNS was demonstrated to accelerate fear extinction in a small study in healthy adults[65] and in a larger study in 42 healthy adults.[66]

Hyperarousal

Hyperarousal is considered a core element of PTSD and is based on the physiological dysfunction in the parasympathetic nervous system. This stems from disordered functioning of the libo-cortical and

peripheral brain networks. taVNS and iVNS have repeatedly demonstrated that they directly impact both systems. To date, only one study has been conducted on hyperarousal in the PTSD population, and it demonstrated consistent increases in parasympathetic response by measuring RSA in multiple postural positions during stimulation.[45] The same study also directly measured hyperarousal response by conducting an emotionally-modulated startle response test, and the taVNS arm of the study far outperformed the control group. This indicates that taVNS does affect hyperarousal as we theoretically expect in the PTSD population, and improvements seen in other patient populations should translate to this group.

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September 8, 2022